KIMMEL ARTTU-SAKARI: SEX AND AGE DO NOT AFFECT TEXTURE ANALYSIS PARAMETERS OF GREY AND WHITE BRAIN MATTER IN HEALTHY CONTROLS

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Tutkimuksessa ”Sex and age do not affect texture analysis parameters of grey and white brain matter in healthy controls” selvitettiin, vaikuttavatko ikä ja sukupuoli terveiden koehenkilöiden harmaan ja valkean aivoalueiden tekstuurianalyysiparametreihin.

Magneettikuvan pikselillä on kirkkautena ilmenevä voimakkuusarvo ja paikka tarkasteltavassa kuvassa. Eri aivorakenteiden pikselit muodostavat ympäröivästä kudoksesta erottuvan oman alueensa, joka ilmenee tekstuurina. Tekstuureista voidaan nähdä paljaalla silmällä patologisia muutoksia, mutta lievimmät aivomuutokset eivät ole ihmisen havaittavissa. Tekstuurianalyysillä voidaan mitata kudoksissa tapahtuvia muutoksia, joita ihmissilmä ei erota.

Populaatiomme koostui 64stä suomenkielisestä verrokista, joilla ei ollut neurologisia, psykiatrisia, neurokirurgisia tai aivotraumaan pohjautuvia sairauksia eikä näkö- tai kuulohäiriöitä. Potilaat kuvattiin magneetilla Tampereen yliopistollisessa sairaalassa. Tarkastelimme 12ta eri aivoaluetta, joihin rajattiin käsin tarkasteltavat alueet. Kaksikymmentä eri tekstuuriparametria laskettiin jokaisesta alueesta MaZda-ohjelmistolla ja tilastollisessa analyysissä etsittiin merkittäviä korrelaatioita parametrien välillä iän ja sukupuolen suhteen.

Havaitsimme, etteivät ikä ja sukupuoli aiheuta tekstuuriparametrien muutoksia tutkituissa aivoalueissa. Tämä helpottaa tulevien tutkimusten suunnittelua potilasrekrytoinnin ja tulosten tulkinnan osalta.

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1 INTRODUCTION

1.1 Texture analysis research

Texture analysis (TA) has been successfully used to detect pathological changes in human brain tissue in a wide range of neurological disorders including tumors (1), stroke (2), multiple sclerosis (3, 4), Parkinson's disease (5, 6) and mild traumatic brain injury (7, 8) to name just a few. Neurodegenerative disorders such as Alzheimer´s disease (9) and psychiatric illnesses have also been investigated (9, 10). TA has also been used to detect spinal cord lesions in multiple sclerosis and TA research on other tissues such as bone, skeletal muscle and lymphatic tissue exists as well. (11)

TA is computer assisted statistical analysis of gray-level dependence between pixels in medical imaging. The underlying idea behind TA is that since pathological changes in tissue can be detected with the naked eye only to a certain extent, we can apply TA to extract statistical textural properties from medical images that are distinct for each illness thus giving us a reliable tool to detect pathology in various tissues even in subclinical phases of disease.

Texture analysis has proven to be a viable method of finding pathological changes in brain structures exceeding the capability of human vision (1-8, 11). Because TA has succeeded in detecting pathological changes in the preclinical phase of some conditions, we must consider the

possibility that TA parameters may be affected by physiological changes caused by aging and they might vary between sexes. Thus, we set out to find whether sex and age affect the TA parameters of healthy controls in order to determine if they affect patient recruitment and research protocols in future TA studies. The logic and fundamental science behind TA is further explained in the "materials and methods" section.

The supporting literature review was conducted using the Ovid® Medline database including all publications from 1949 to present day. The scientific reasoning behind textures, their features and their computation is based on the book Texture Analysis for Magnetic Resonance Imaging by Hajek et al. (11).

1.2 Whole brain, cortical and grey matter findings

In addition to pathological states, studies with conventional and specialized MRI have shown measurable physiological differences in the brain both in relation to aging and between sexes. The main known effect on the whole brain is total volume reduction and cortical atrophy (12, 13). Total brain volume reduction was detected already in mid-life in a Finnish population, the total volume reduction was greater in women and the distribution of volume reduction on cortical areas differed between sexes (13).

Differences in regional cerebral cortex thickness between sexes and age groups have been found to exist. (12, 14) Men have shown larger average total brain volumes (due to the larger anatomical size of the cranium) than women, but subcortical structure size correlates more with brain size than with sex and results from various studies comparing the properties of subcortical structures between sexes are still conflicted. (15)

Cortical glucose hypometabolism with atrophy caused by aging has also been documented combining MRI and positron emission tomography (PET), the manifestation of these changes differed between sexes and were limited to ages under 66 after which they became indistinguishable. (12)

In subcortical brain gray matter areas some changes have been found to develop as a result of the normal aging process, of which atrophy is the most common (16-18). Iron deposition in subcortical gray matter structures has also been found to vary with age and sex (18). Reviewed research data on pontine and substantia nigra lesions did not give data on age and sex differences as they were limited to specific pathological states.

1.3 Research on white matter

Studies with advanced MRI techniques such as diffusion tensor imaging (DTI), fractal geometry texture analysis and Resting-state functional magnetic resonance imaging have found that that the normal aging process in healthy adults causes changes in subcortical white matter tracts (19-22). White matter pathways have been found to mature and degenerate at varying rates between sexes across the whole human lifespan (22).

Anatomical sexual dimorphism has been observed in in white matter pathway organization (21). Furthermore, it has been shown that as male and female subjects age, the localization of the changes in white matter connections running between both cortical tissue and deep brain gray matter are differently distributed between sexes. (19-21)

As of yet, no studies exist where TA is applied in order to determine whether age and sex inflict physiological changes on brain white and gray matter areas that can be measured with TA

parameters. In this light, it is sensible to determine if such a link exists as it might affect the recruitment of present and future TA research and how patient data should be analyzed.

Thus the primary hypotheses to be tested were defined as “Aging causes changes in brain grey and white matter structures measurable by TA parameters” and “Anatomical differences in grey and white brain matter exist between men and women, verifiable using TA parameters.”

2 MATERIAL AND METHODS

2.1 Patient group

64 healthy adults were included in the study. All had been previously recruited into TA research and our population was gathered from the pre-existing pool of patient data and their medical images. All patients have served as healthy controls in previous TA studies. Of these, 27 were males and 37 females. The subjects were aged between 20 and 60 years with a standard deviation of 11,7 years. None of the participants showed significant structural brain abnormality in conventional MRI sequences. Exclusion criteria were:

1. neurological problems including any neuroimaging abnormality
2. psychiatric problems
3. history of traumatic brain injury
4. former neurosurgical procedure
5. impairment of hearing, vision or both

6. first language other than Finnish
7. Any MRI contraindication
8. refusal to participate

No grave structural anomalies were found in the MRI images obtained in this study that would have led to the exclusion of patients. The patient data was numerically coded and the researcher was not aware of the ages and sexes of the patients prior to the statistical analysis phase to ensure the reliability and objectivity of the study. The study was conducted at Tampere University Hospital.

2.2 Magnetic resonance imaging

In magnetic resonance imaging, the protons within the examined object or tissue are excited by an oscillating magnetic field or radio frequency pulses and as they return to a relaxed state, they emit a radio frequency signal that can be localized by coils that are switched on and off in rapid succession. In medical imaging, MRI produces “slices” of the human body in a preferred plane (axial in this case) consisting of volume elements called voxels, each with a locus and intensity value. The slices are usually a few millimeters thick.

An individual voxel is displayed as a two dimensional square element, called a pixel. Each pixel expresses the obtained signal intensity as a numerical value (0-255 if 8 bits of information is stored per pixel) and this is represented visually on a grey scale ranging from 0 (total darkness, black) to 255 (maximum brightness, white). As these pixels of varying intensity value are displayed on screen with their localization on the x-y scale, we obtain a medical image of the desired anatomical area and we can extract information from it using our vision and computer assisted mathematical methods if needed.

In our study, magnetic resonance imaging was done on a 3T Siemens TrioTim device (Erlangen, Germany) with a 12-channel head matrix coil following a clinical procedure. The sequence used was axial 2D turbo spin echo. Imaging parameters were: repetition time 5790 ms, echo time 109 ms, slice thickness 4.0 mm with 5.2 mm gap, matrix size 448 x 326 pixels, field of view 230 mm and a flip angle of 120°.

2.3 Image analysis

Having obtained the MRI image, we can discern anatomical structures from the whole brain using our eyesight and knowledge of existing brain anatomy. Each of these structures can be described as an area within the image that has distinct visual features separating it from surrounding tissues. This kind of area is called a texture. The texture perceived is a product the physical properties of the material under investigation, in the case of MRI, the proton density or relaxation time of the excited protons of the tissue.

Human vision alone can extract several features from the so called sub-patterns that are repeated within the texture that give rise to descriptions such as smoothness, coarseness, brightness, regularity, randomness of the texture´s general appearance. However, the theory behind texture analysis postulates that textures contain within them much more information than can be detected or described by human capabilities and TA can detect and describe this information quantitatively. This has been shown in practical experiments on human tissues. (11)

As the physical properties of the object or material being investigated change, the textural properties of its surface or interior change as well and these changes can be quantitatively measured by TA. This carries over to the practical application of TA in medical imaging: as pathology causes changes in cellular and tissue structure this causes the textural properties of the

medical image obtained from that tissue to change as well and this can be quantified by TA even in early stages of pathology even before human vision can detect them.

Due to the random localisation of the ROIs in the MRI image and the background noise pattern created by the MRI apparatus, each voxel/pixel is treated as a random variable and thus the TA parameters are calculated using statistical methods. From each ROI containing a certain number of pixels with their individual grey-level intensity values, a first order (examines single pixels) histogram is drawn denoting how many pixels of which intensity value are found within the ROI (number of pixels on the y scale and the intensity values on the x-scale). (11)

From the histogram obtained, basic parameters such as mean, variance, skewness and kurtosis can be obtained. The mean describes the average intensity level of the image and the variance is the amount of intensity difference around the mean. Skewness approaches zero the more the histogram is symmetrical about the mean (a Gaussian distribution, for example) and is positive or negative if there are more values above or below the mean. Kurtosis describes the flatness of the histogram. (11)

Mean and variance can only be used as TA parameters if the images are normalized as they are otherwise affected more by the properties of the MRI image acquisition process (such as general brightness of the image) instead of the properties of the textures examined. (11) Thus, in order to minimize the influence of contrast variation and brightness of each MRI image, grey level normalization was done for each ROI. This was done using a method which normalizes image intensities in the range of $[\mu-3\sigma, \mu+3\sigma]$, μ representing the mean grey level value and σ the standard deviation. This method has also been used in previous TA studies of senior researchers. (23)

These first order parameters obtained from the values of single pixels do correlate with the visual appearance of the texture under analysis, but don´t give us much more information about the texture than what can be seen with the naked eye. (11)

In order to extract even further textural properties and changes unseen by human vision, second order statistical methods are used. The reigning method in TA today is the co-occurrence matrix method. This method examines the grey-level intensity dependencies between two pixels within the ROI. The co-occurrence matrix (COM) is formed by determining the pixel pairs separated by a set distance along a set orientation (angle) that have correlating intensity values. The TA parameters are calculated from the matrix formed by the correlating pixel pairs. If all of these correlating pixels along all distances were involved in the calculations, it would provide an overwhelming amount of data that would prove too cumbersome to analyse and therefore pixel pairs are examined over a set distance of one pixel. The orientations between pixel pairs are fixed as well. Furthermore, intensity values are normalized as 0-255 to speed up calculations while sacrificing some accuracy. The run-length matrix (RLM) also investigates pixel pairs. Detailed mathematical methods of the COM and RLM matrices and each TA parameter are not explained in this report for practical reasons.

20 separate TA-parameters were calculated by MaZda software (24-26) for each ROI. The first four were first order histogram based parameters mean, variance, skewness and kurtosis. 11 parameters were COM based: angular second moment, contrast, correlation, sum of squares, inverse difference moment, sum average, sum variance, sum entropy, entropy, difference variance and difference entropy. The final five parameters were RLM based: run-length nonuniformity, grey-level nonuniformity, long-run emphasis moment, short-run emphasis moment and fraction.

The COM and RLM parameters compare two adjacent pixels with one another. Both COM and RLM parameters were calculated vertically, horizontally and diagonally (toward angles 0°, 45°, 90°, and 135°) using eight bits per pixel (each pixel has an intensity value from 0 to 255). All four directional values of each parameter were averaged into a single parameter to ensure the reliability of the analysis because there is no way to ensure that the patient undergoing MRI is in

an exactly straight position nor is there any way to define what is absolutely “straight” in an anatomical sense as no living organism of this size is perfectly symmetrical.

2.4 Regions of interest

Regions of interest (ROIs) were selected to be well defined grey and white matter structures reaching from the midbrain to the cerebral cortex on which circular ROIs were placed and drawn by hand on both hemispheres. All ROIs were sized 10x10 or 15x15 in diameter both for practical reasons (they fit snugly into the anatomical brain areas investigated) and to obtain the most

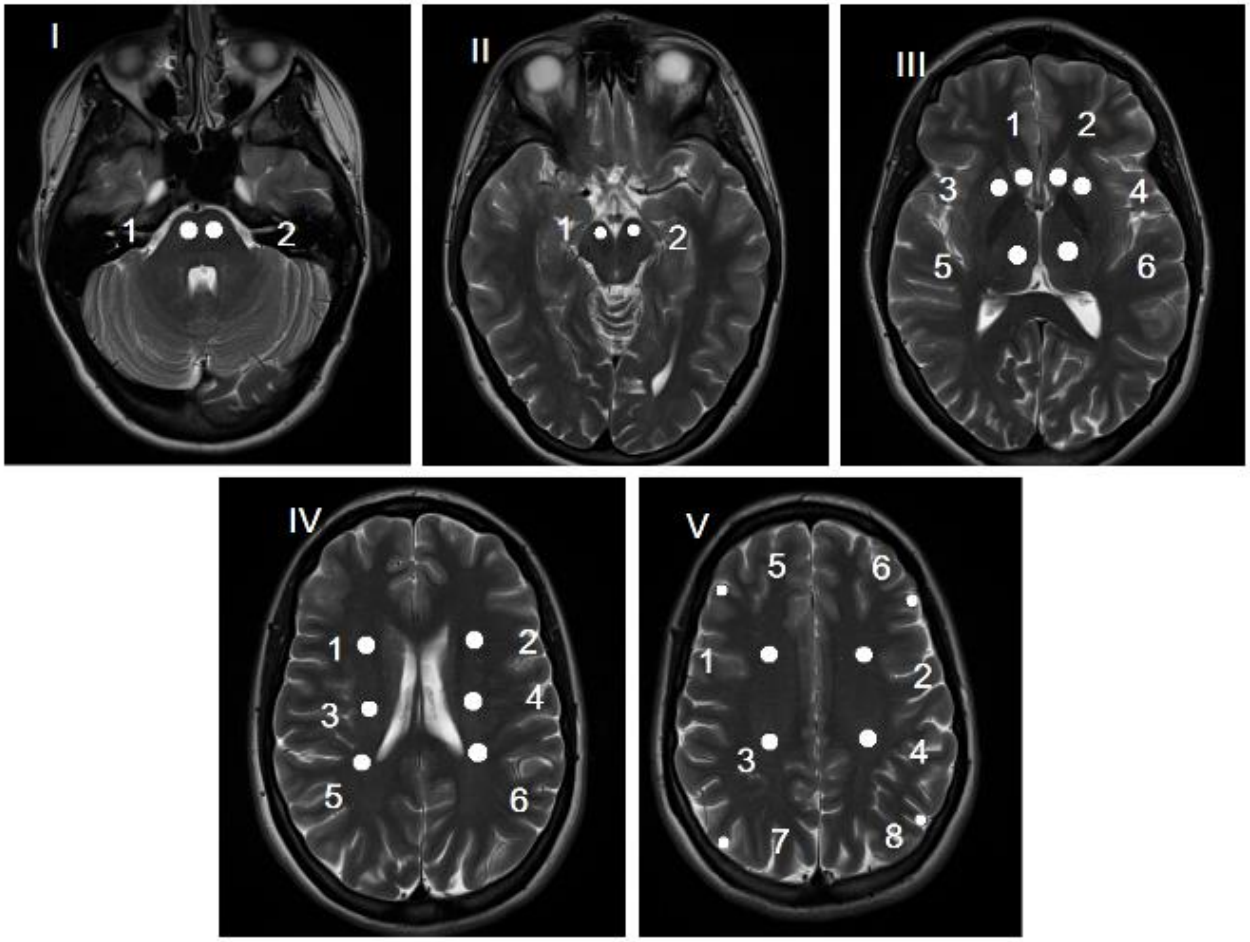

Figure 1. MRI levels (I-V) and ROIs, further explained in table 1.

Table 1.	Level	ROI 1	ROI 2	ROI 3	ROI 4	ROI 5	ROI 6	ROI 7	ROI 8
MR image levels and regions of interest (ROI). Image levels and ROI's are presented in Fig. 1. ROI sizes are braceted, size in pixels. All ROIs are circular.	I	Basilar Pons dex 15x15	Basilar Pons sin 15x15						
	II	SN pars compacta dex 10x10	SN pars compacta sin 10x10						
	III	Nucleus Caudatus dex 15x15	Nucleus Caudatus sin 15x15	Putamen dex 15x15	Putamen sin 15x15	Thalamus dex 15x15	Thalamus sin 15x15		
Dex, dexter; sin, sinister; ant, anterior; med,medial; post, posterior.	IV	Corona radiata ant dex 15x15	Corona radiata ant sin 15x15	Corona radiata med dex 15x15	Corona radiata med sin 15x15	Corona radiata post dex 15x15	Corona radiata post sin 15x15		
SN, substantia nigra	V	Centrum semiovale ant dex 15x15	Centrum semiovale ant sin 15x15	Centrum semiovale post dex 15x15	Centrum semiovale post sin 15x15	Cerebral cortex ant dex 10x10	Cerebral cortex ant sin 10x10	Cerebral cortex post dex 10x10	Cerebral cortex post sin 10x10

reliable statistical data as possible because varying ROI sizes affect statistical analysis adversely (23).

The ROIs under investigation were chosen to be clearly defined gray and white matter structures that are known to be affected by known pathological states. These were basilar pons, substantia nigra pars compacta, nucleus caudatus, putamen, thalamus, anterior, medial and posterior corona radiate, anterior and posterior centrum semiovale and anterior and posterior cerebral cortex.

The levels and ROIs are highlighted in Figure 1 and Table 1 in greater detail. ROI's that grossly transgressed their intended brain structure or overlapped with other brain areas were omitted.

2.5 Imaging software

The whole TA process was done using MaZda software version 4.6.2.0 (24-26): the MRI image levels containing the desired anatomical structures were ported into the program, the ROIs were defined and placed by hand using MaZda´s in-program tools and finally the TA parameters were calculated separately for each level and stored as a single data set with the patient data.

MaZda is a shareware program for calculation of texture parameters of digitized images. It was developed at the Institute of Electronics, Technical University of Lodz, Poland by Michal Strzelecki and Piotr Szczypinski for researchers in the COST B11 European Project "Quantitative Analysis of Magnetic Resonance Image Texture". It was then released publicly to be a beneficial tool for everyone participating in TA research. It is available online for free download for MS Windows® operating systems. The code is written in C++ and Delphi©. (24-26)

2.6 Statistical analysis

As all 20 TA parameters were calculated from the 15 ROIs on 5 MRI levels it was a rather straightforward matter of calculating whether any of the parameters of any ROI showed correlation to age or sex and was this correlation statistically significant.

Research data was statistically analysed using IBM SPSS (Windows version 22.0. SPSS Inc. Chicago, IL, USA). T-test was applied to determine possible TA parameter differences between sexes. Correlations between age and TA parameters were calculated with both Spearman's and Pearson's correlations. Correlation coefficients >0,5 and <-0,5 with P value <0,05 were considered statistically significant.

3 RESULTS

3.1 Sex

No significant negative or positive correlations that were also of statistical significance were found between sexes and their TA parameters in any of the brain structures in this study. Thus our hypothesis that sexual dimorphism of the investigated brain areas detectable by TA parameters is void.

3.2 Age

No significant correlation, positive or negative, between age and TA parameters were found in any of the ROIs investigated. All correlation coefficients were between -0,5 and 0,5. Therefore the hypothesis that aging causes changes in the textural properties of the brain areas examined can be rejected as well.

4 DISCUSSION

At first glance, to find no significant difference in TA parameter behavior in the grey and white matter areas under investigation between sexes and in relation to age is a welcome result, yet there are some issues that have to be taken into consideration.

Some correlations of statistical significance ($P < 0,05$) were found in the putamen of the right hemisphere and the ROIs of substantia nigra of both hemispheres in the TA parameters contrast, correlation and difference variance, but they were all either just below -0,5 or above 0,5 and therefore beyond being mathematically significant. Considering the nature of the statistical methods used and findings in previous studies, these TA parameters are related more to imaging aspects such as overall “brightness” or image intensity and noise than the properties of the tissue under investigation (11, 23). Also, even though the left and right hemispheres carry out different tasks, it seems rather unlikely that any single subcortical brain structure on a single hemisphere would exhibit such TA behavior when other structures on both hemispheres do not.

4.1 Cortical findings

Obvious technical difficulties arose concerning the cortex. Although the contrast between the cortex, the overlying subarachnoid space and the white matter beneath it is significant and therefore they can be easily distinguished from each other, the cortical layer is simply so thin that the ROI's placed in order to investigate it were not very functional as even small 10x10 ROIs almost invariably overlapped both cerebral grey matter and either the subarachnoid space or the underlying white matter in nearly every case by a few pixels. Naturally, this gives unreliable results, as including two areas of grossly differing contrasts into a single ROI offsets the calculation of TA parameters, as the statistical co-occurrence matrix method assumes that the texture under analysis is homogenous (11). Therefore, even though cortical areas did not show any statistically significant correlations this could have been easily disputed had they done so. This issue became apparent during the placing of the ROIs yet their calculations were carried out just in case to see whether any correlations could be found despite this.

Currently, placing ROI's on the very thin layer of cerebral cortex by hand is quite impractical and unreliable and drawing freehand ROIs along the cortex would be cumbersome. This might change if some other method emerges, perhaps in the form of automatic software or advancements in imaging hardware and software technology.

4.2 Basal ganglia and pons

When investigating the male and female brain it is not surprising that the basal ganglia showed no sexual dimorphism in our study as previous research has only found that they differ only in size and in relation to total brain volume which is greater in males on average.

However, taking the aging process into account it is somewhat surprising that TA parameters of the basal ganglia remained unaffected as previous studies have found changes in iron deposition and atrophy in them as a product of age.

Further research should be conducted on gray matter areas combining TA with DTI or other imaging techniques to determine what are the products of age and sex on these structures and why TA parameters are unaffected by them. Still, in this light, our study supports the application of TA as a valid method to investigate pathologies affecting the basal ganglia and facilitates the recruitment of patient material and design of future TA research concerning these areas.

4.3 White matter

It is the lack of intersexual and age related difference within white matter of the corona radiata and centrum semiovale that raises further questions worth investigating.

Since it has been shown by DTI studies that white matter organization is not only generally different between sexes but the connecting tracts between basal nuclei and cortical structures also develop and atrophy at varying rates between men and women along the lifespan it must be

asked why no TA parameters showed significant changes in our study to reflect this? These previous DTI findings were obtained from a patient group ranging from childhood to geriatric ages which covers a broader age spectrum than our patient material yet similar results were also evident in studies investigating patients in midlife - an age group that is well represented in our study.

There are several possible explanations for this. The most obvious one is that it is practically impossible for TA parameters to detect existing sex and age dependent differences in white matter tract organization due to the fact that as only slices from two levels on the axial plane are under scrutiny, they are displayed in a two dimensional layout and therefore all the individual tract bundles cannot be identified and observed separately. Thus the whole distance of these three dimensional pathways from one gray matter structure to another cannot be covered and their properties measured by TA.

Furthermore, as the 15x15 ROIs placed on the corona radiata and centrum semiovale enclose within them both the actual white matter nerve bundles within the area and all accompanying supportive brain tissue with them, the TA parameters calculated do not in any way distinguish between these two and cannot therefore characterize the properties of the nerve tracts but treats the area more as bulk tissue. Even individual MRI pixels are in the order of millimeters and are the sum of countless cellular structures, whereas histology-level neuronal structures can be examined in the order of micrometers.

Another potentially discouraging explanation is that perhaps TA parameters calculated from ROIs laid out in this fashion simply cannot detect existing changes in white matter areas. Even if this were the case, we do know that TA can detect MS lesions from the spinal cord, it can distinguish between healthy brain structures and a great number of neurological disorders affecting them and it can, in some cases, detect changes in preclinical phases of disease. It seems that the changes occurring in brain grey and white matter as a function of age and sex simply manifest in ways that do not affect textural properties of the tissue but can be detected by other imaging methods.

Taking all previous white matter research into account, the outcome that the textural properties of the investigated white matter areas didn´t differ between men and women nor patients of different ages can be seen as somewhat surprising. However, this is not so upsetting considering that possessing the ability to define the nature of white matter connectomes is not even the goal of TA, which deals solely in the properties of two dimensional textures. Therefore, the possible limitations of TA do not undermine the importance of our results: Despite what reason, since TA parameters of healthy controls remain unaffected by age and sex these results are very beneficial for existing and future TA research as they are off the list of possible confounding factors.

4.4 The age factor

Irrespective of sex and the structures being analyzed there are aspects worth further illumination regarding age and the textural properties of the brain. It is well known that neuroplasticity, the capability to obtain and store new information, general learning ability and motor skills are all adversely affected by normal aging. Conversely, the skills learned and knowledge accumulated during a lifespan affect the brain as well. It is also known that atrophy occurs as a product of aging in cortical and subcortical areas and the integration of white matter connections between these areas are subject to change as well even before the clinical manifestations of old age are apparent. Also, previous TA research has detected preclinical lesions in some brain areas. Therefore, one could have expected some changes to be presented by the textural behavior of the areas analyzed in this study.

Then again, a healthy patient at 60 years of age isn´t considered medically old as such and can perform some tasks requiring cognitive and motor skills even more fluently than a 20-year old individual depending on individual genetic potential and proficiency.

To clarify this, TA research could be paired with standardized neuropsychiatric and geriatric testing to see what level of impairment could cause TA parameters to shift in brain tissue and at what age do these changes occur, if they occur at all.

As we reasoned with grey and white matter findings, the fact remains that as age and sex do not alter textural properties of the brain areas investigated, at least on the behalf of the basal grey areas and white matter, the validity of TA is upheld by our results.

4.5 Strengths

Despite its limitations, there are several strengths in our research protocol and the application of MRI texture analysis on brain study.

Although the eldest of the participants was only 60 years old and thus this study does not extend into medically geriatric or pediatric patient groups, recruiting larger, more heterogenic populations for further studies should be relatively easy as patients undergo a single session of non-invasive imaging without being subjected to ionizing radiation. This form of harmless and painless research demands less ethical consideration than ionizing, isotope and invasive methods and should lower the threshold of participation from the patient´s standpoint.

Furthermore, image analysis with MaZda Software has a gentle learning curve and can be done by researchers from different fields of science; engineers, physicians and medical students to name a few. All of this makes this research highly repeatable.

Looking onward it would be useful to compare and pair TA findings with other imaging modalities and structured neuropsychological surveys. We could continue research on patients on an even larger age scale (pediatric to geriatric), patients with varying backgrounds and demographics, medical conditions, systemic illnesses and so on to find whether they affect TA data of brain areas that are of interest in neurological pathology. If they do not, the inclusion criteria for future studies will be even more forgiving thus facilitating patient recruitment and future research design. This would also further solidify the role of texture analysis as a robust method of detecting brain pathology even within heterogeneous patient groups. According to our findings thus far this is the case.

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